Antipsychotic Medications

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Antipsychotic Medications

- What you need to know…
- And maybe some of what you don’t.

History

“In 1952, Henri Laborit, a surgeon in Paris, was looking for a way to reduce surgical shock in his patients. Much of the shock came from the anaesthesia, and if he could find a way to use less, his patients could recover quicker. He knew that shock was the result of certain brain chemicals and looked for a chemical that might counteract these. He tried antihistamines, usually used to fight allergies.” (cont)

History

He noticed when he gave a strong dose to his patients, their mental state changed. They didn't seem anxious about their upcoming surgery, in fact, they were rather indifferent. Laborit was able to operate using much less anaesthetic. He was so struck by the effect on his patients, especially with a drug called chlorpromazine (trade name Thorazine) he thought the drug must have some use in psychiatry. But at that time, "no one in his right mind in psychiatry was working with drugs. You used shock or various psychotherapies," said Canadian psychiatrist Heinz Lehmann. Laborit kept pressing his point, however. A fellow surgeon passed the word to his brother-in-law, the psychiatrist Pierre Deniker. Deniker's interest was piqued and he ordered some chlorpromazine to try on his most agitated, uncontrollable patients.

History

- Outcome
  - Immediate “cures”, agitated and catatonic patients could be treated in a quick and more realistic fashion.

Neuroleptics

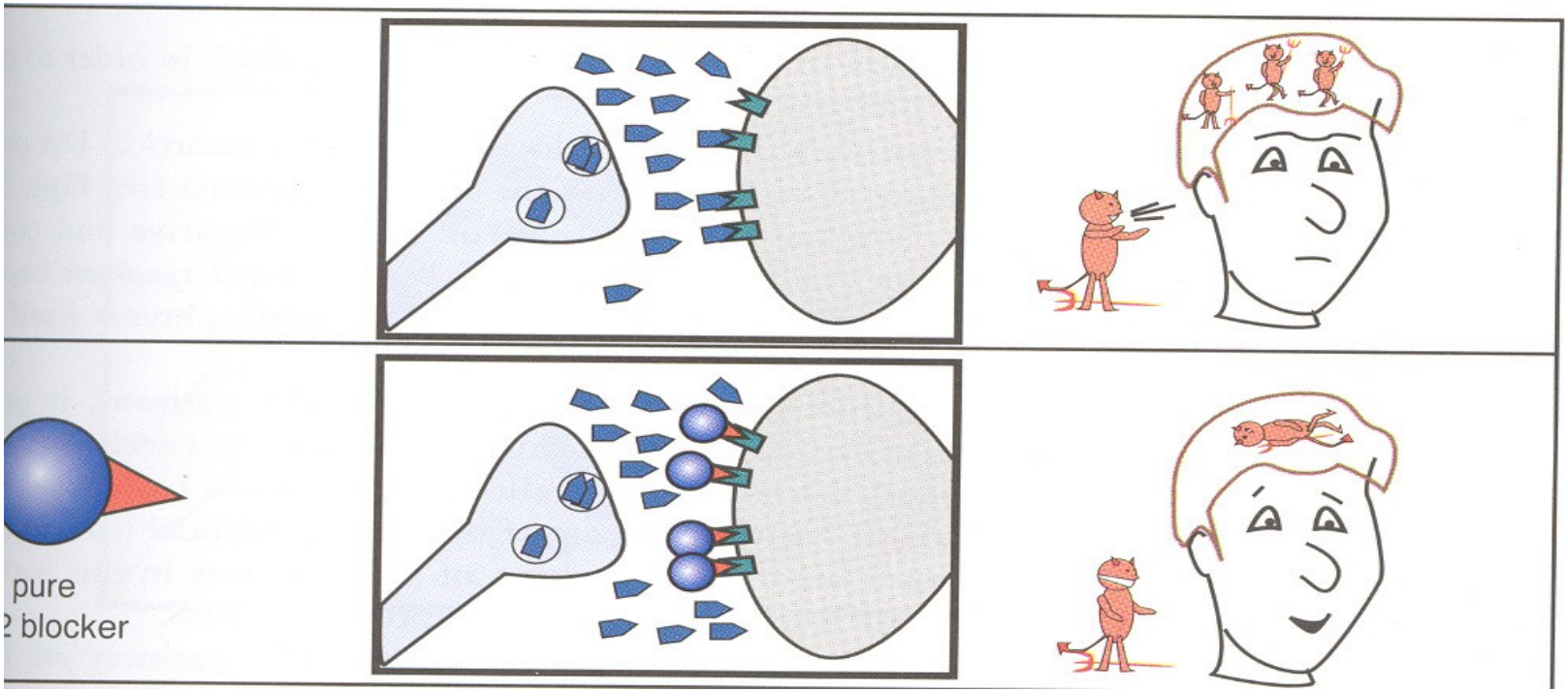
- Hence NEUROLEPTICS were formed!
- Neuroleptics, what the heck is that?
  - French neuroleptique :
  - **neuro**-, ***nerve*** (from Greek.)
  - **leptique**, ***affecting*** (from Greek.)
- Essentially it is a state characterized by psychomotor slowing, emotional quieting, and affective indifference.
  - Sounds like negative symptoms to me…

Biochemistry

- Thought you left this behind, huh?
- Mechanism of action
  - Dopamine 2 Receptors(dopamine hypothesis for schizophrenia)
    - D2 blockers, block the effects of dopamine in the mesolimbic dopamine pathway

Dopamine Theory of Psychosis

- That's a "pure D2 blocker"
- Top is psychotic guy
- Bottom is not psychotic guy



Dirty, Dirty Drugs

- Unfortunately, these medications are not selective as to location of action
  - Mesocortical
    - Cognitive deficits, aforementioned “neurolepsis.” Looks like the negative symptoms of schizophrenia, ironically.
  - **Nigrostriatal**
    - Extrapyramidal system-EPS-
    - TD thought to be long term up regulation because of dopamine blockade

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Dirty, Dirty Drugs

- Tuberoinfundibular pathway
  - Dopamine has a second name it's called…
    - Prolactin Inhibitory Factor
    - So if you block(negative) an inhibitor(double negative) you get an increased effect

Dirty, Dirties

- So pure D2 Blockers also cause
  - Hyperprolactinemia
    - WOMEN
      - Galactorrhea, amenorrhea
    - MEN
      - Sexual dysfunction and weight gain
      - Remember in “A Beautiful Mind” when Russell Crowe couldn’t perform his “husbandly duties?”

Hi’s and Low’s

- Dopamine and Acetylcholine(muscarinic style) have reciprocal relationship in **nigrostriatal** pathway.
  - Dopamine suppresses acetylcholine activity.
  - So utilizing older antipsychotic medications with potent anticholinergic effects, and you will reduce EPS from **nigrostriatal** pathway.

Hi’s and Low’s

- Alternately you can add an anticholinergic like:

  Diphenhydramine(Benadryl)
  Benztropine(Cogentin)
  Trihexyphenidyl(Artane)

Conventional's continued…

- These drugs are often even "dirtier" in that they often affect:
  - Alpha 1 adrenergic
    - Like doxazosin can cause orthostatic hypotension
  - Histamine 1
    - Think any variety of seasonal allergy medications

Which are what?

- High Potency (high EPS, less anticholinergic, less hypotension, low equivalent dose (<5mg))
- Haloperidol
- Thiothixene
- Fluphenazine
- Mid Potency
- Molindone
- Loxapine
- Low Potency (low EPS, ++anticholinergic, high equivalent dose (>40mg)
- Chlorpromazine
- Thioridazine

Table

Wake up!

- Okay change gears before we get to the new and clinically relevant drugs you'll see used most often
- Let's do the Side Effects

Side Effects

- Q:What is most important?
- A:What’s going to kill them…

Side Effects

We discussed earlier the most clinically “scary” side effects all involve the nigrostriatal pathway.

So all of the nigrostriatal pathway involve muscle movement “badness.” Don’t you remember all those neurophys lectures on Parkinsons?

Side Effects

- Muscle “badness” #1-dystonias
  - Which things if dystonic would be very upsetting to both patient and physician?
  - Laryngeal spasm, oculogyric crisis are the relatively common medical emergency dystonias that are reported.
  - Also common though not life threatening is torticollis.
  - Dystonias can involve any muscle group.

Side Effects

- Treatment of dystonias
  - What have we learned?
  - What SHOULD be the treatment?
  - How is it usually given in this situation?
  - What commonly used drugs by ER, Surgery, Internal Medicine, FP, and OB/GYN doctors can often cause dystonias? (they are phenothiazines)

Side Effects

- Akathisia
  - Internal feeling of restlessness
  - Sometimes gets acted out it’s so intense
  - Usually it happens soon after initiation or increase in dose of medication
  - Treatment
    - Decrease dose
    - Beta-Blockers, low dose Benzodiazepines
      - *You can use anticholinergics, but considered 3rd line treatment
    - Change to a different antipsychotic when possible

Side Effects

- Parkinsonian syndrome
  - Looks like Parkinson's disease
    - Any idea why?
  - Create a deficiency of dopamine in the nigrostriatal pathway
  - Remember *rabbit syndrome*
    - This is NOT TD, important point
  - Treatment is reduce dose and use medications which increase dopamine(amantadine) and again anticholinergics
    - Switch meds

Side Effects

- Tardive Dyskinesia(TD)
  - Disorder characterized by involuntary choreoathetoid movements of the face, trunk, or extremities.
  - Approximately 1% per treatment year of conventional antipsychotics.

TD

- Ironically will improve if you increase the dose of antipsychotic, however
  - You will not be able to decrease dose without symptoms getting worse
- So treatment is to decrease dose, switch meds
- You can actually treat with clozapine
- It is now less of an issue than in the past because of the atypical antipsychotics
- Remember your AIMS tests at onset of therapy and at least yearly after that

NMS

- Neuromuscular Malignant Syndrome
- “Lead pipe” rigidity
- Medical Emergency
- ICU
- Supportive treatment initially
- Bromocriptine and Dantrolene(not good EBM supporting these, but they are what we use)

Others

- QT-interval prolongation-Haloperidol, and most of the newer atypicals
- Weight Gain-Olanzapine is the “Big Daddy” of this side effect. Has been correlated(no clear causal connection) with DM 2
- Sensitivity to sunlight
- Increased LFT’s
- Transient leukopenia, neutropenia, and even agranulocytosis(clozapine)
- Decreased seizure threshold

Clozapine

- First “atypical” antipsychotic (AAP)
- Mechanism of Action
  - Mostly D2 and 5HT2A blockade
  - It has something for everybody however
- Notes
  - Agranulocytosis-1-2% incidence. Life threatening. Check CBC every 2 weeks.
  - Works when others don’t. Occasionally have “awakenings phenomena”
  - Best for negative symptoms
  - Does not cause, and can even treat, TD
  - Weight gain almost the worst among antipsychotics
  - Greatly reduces seizure threshold

Risperidone

- High doses acts like a conventional

Olanzapine

- Weight gain is significant
- Has significant mood altering properties, and has a first-line indication for bipolar disorder

Quetiapine

- Virtually no EPS
- No prolactin elevation
- Q-T interval bandit

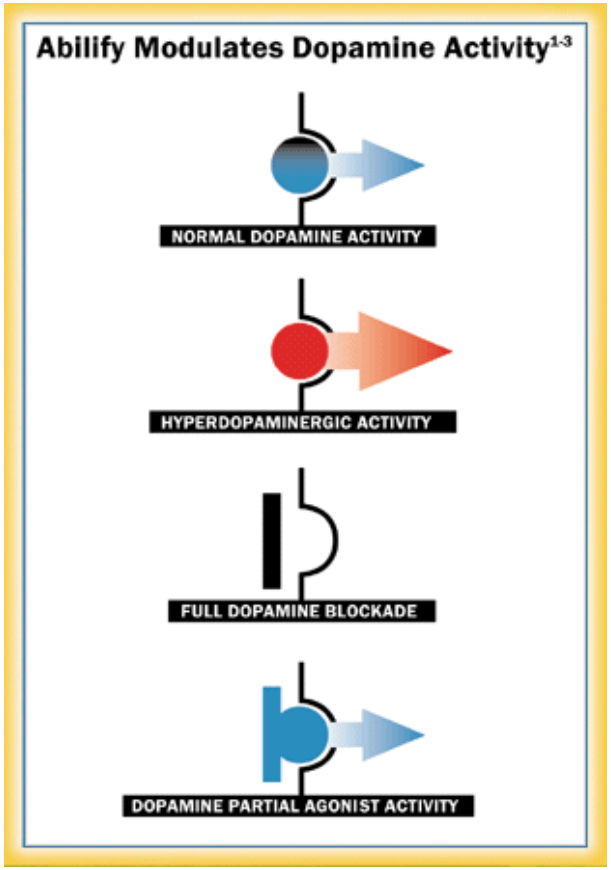
Ziprasidone

- Little to no weight gain

Aripiprazole

- Abilify™ (aripiprazole) is a partial agonist that uniquely modulates dopamine activity
- Functional antagonist activity at D_2 receptors in a hyperdopaminergic environment
- Functional agonist activity at D_2 receptors in a hypodopaminergic environment
- Abilify has serotonin **antagonist** activity at 5-HT_{2A} receptors and **partial agonist** activity at 5-HT_{1A} receptors.
- Abilify has **moderate affinity** for alpha$_1$-adrenergic and histamine (H_1) receptors.
- Abilify has **no appreciable affinity** for cholinergic muscarinic receptors.

Aripiprazole



- The mechanism of action of Abilify, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of Abilify is mediated through a combination of partial agonist activity at dopamine D_2 receptors and serotonin $5HT_{1A}$ receptors, and antagonist activity at serotonin $5HT_{2A}$ receptors. Partial agonism refers to the ability to both block a receptor if it is overstimulated and to stimulate a receptor when activity is needed.

Anxiolytics

- Benzodiazepines
  - Facilitate the inhibitory properties of GABA.
    - Increases the endogenous properties of GABA, which result in an opening of chloride ion channels and a decrease in neuronal excitability.

Benzo’s

- Short acting
  - Alprazolam, lorazepam, oxazepam
- Long acting
  - Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam

Cross-Tolerance

- Alcohol and barbituates also work through GABA mediated processes
  - You can withdraw with benzo’s
  - You can develop cross-tolerance with benzo’s
  - Often the sedative effects will become tolerant, however anxiolytic properties remain
  - Disinhibition!

Buspirone

- Agonist at the 5-HT1A receptor
  - Not GABA mechanism
  - No cross tolerance
  - Suppresses neuronal firing in the dorsal raphe through autoreceptor stimulation
  - SAFE
  - Efficacy??

Zolpidem

- Nonbenzo, Benzo
- Works at a subunit of benzodiazepine receptor
- Short acting(1 hour half-life, hence AM-Bien)

What else?

- Essentially ALL antidepressants have been shown to have long term anxiolytic effects compared to placebo(Upwards of 80% response rate)

Others

- Specific phobia-beta blockers, benzo’s
- OCD-SSRIs

Generic (trade) name	Usual daily dosage (mg)	Methods of administration	Available oral doses (mg)	Approximate oral dose equivalents (mg)[a]
Conventional antipsychotics				
Phenothiazines				
1 Chlorpromazine (Thorazine)	300–600	po, im	10, 25, 50, 100, 200	100
Piperidines				
2 Thioridazine (Mellaril)	300–600	po, im	10, 15, 25, 50, 100, 150, 200	100
3 Mesoridazine (Serentil)	150–300	po	10, 25, 50, 100	50
4 Pimozide (Orap)	2–6	po	2	1–2
Piperazines				
5 Trifluoperazine (Stelazine)	15–30	po	1, 2, 5, 10	5
6 Fluphenazine (Prolixin)	5–15	po, L, im, D	1, 2.5, 5, 10	2
7 Perphenazine (Trilafon)	32–64	po	2, 4, 8, 16	10
Thioxanthenes				
8 Thiothixene (Navane)	15–30	po, L, im	1, 2, 5, 10, 20	5
Butyrophenones				
9 Haloperidol (Haldol)	5–15	po, im, D	0.5, 1, 2, 5, 10, 20	2
Dibenzoxazepines				
10 Loxapine (Loxitane)	45–90	po	5, 10, 25, 50	15
11 Molindone (Moban)	30–60	po	5, 10, 25, 50, 100	10
Atypical antipsychotics				
Clozapine (Clozaril)	250–500	po	25, 100	50
Risperidone (Risperdal)	4–6	po	1, 2, 3, 4	1
Olanzapine (Zyprexa)	10–15	po	2.5, 5, 7.5, 10	2–3
Quetiapine (Seroquel)	300–400	po	25, 100, 200	100

Note. D = long-acting decanoate preparation; im = short-acting intramuscular; L = liquid; po = oral tablets or capsules.

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